REMARKS

Upon entry of this amendment, claims 28-59 constitute the pending claims in the present application. Applicants have added new claims 52 - 59 to clarify the subject matter claimed. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Election / Restriction

Applicants note that claims 28, 33-38, and 43-45 are withdrawn to the extent they read on non-elected species BMP-2, BMP-5, BMP-6, and 60A. In view of the argument below regarding species election in Markush group claims, Applicants respectfully point out, however, that pursuant to MPEP 803.02, "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended." Accordingly, if the prior art rejections are withdrawn, these claims should be considered throughout their scope.

Claims 37-42 and 49-51 are withdrawn from consideration as being directed to a non-elected invention.

Claim Objections

Claims 28 and 37-38 are objected to as reciting an improper Markush group. In support of this objection, the Office Action cites MPEP 803.02:

"Since the decisions in *In re Weber*, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and *In re Haas,* 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. *In re Harnish*, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and *Ex parte Hozumi*, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility."

Applicants have amended claim 28 to recite a proper Markush group. Applicants submit that amended claim 28 does not lack unity of invention in view of the above cited MPEP passage, and thus the Markush group in the amended claim 28 is not improper. First of all, all polypeptides (of the original claim 28 and of the current amended claim 28) share a common utility – the ability to stimulate dendritic outgrowth and synapses formation. Secondly, all these polypeptides share a substantial structural feature – the C-terminal six- or seven-Cys skeleton structure, which is recited in the claim and disclosed as being essential to the utility. Thus, by definition, unity of invention exists for all polypeptides included within the Markush group.

Furthermore, even if the Examiner were to maintain the original restriction requirement, Applicants submit that the restriction requirement pertains to restriction of the Markush group. Pursuant to MPEP 803.02, "If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. In such a case, the examiner will not ... require restriction." Since the amended claim 28 contains only a few Markush group members, the Examiner must examine all members without restriction, regardless of whether such individual members are directed to independent and distinct inventions.

Even if a restriction is still imposed, the same section of MPEP states that "...where two or more of the members are so unrelated and diverse ... the examiner may require a provisional election of a single species prior to examination on the merits ... Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability...[S]hould no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. ... The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim." (emphasis added). Therefore, in the case where no prior art is found during the initial search of the *provisionally* elected Markush species (as is the case during the previous round of examination), the Examiner must extend the search to other initially *nonelected* polypeptide species, to the extent necessary to determine patentability.

The Office Action refers the Applicant to the enablement rejection of record, and states that since the specification allegedly does not provide enablement for polypeptides other than the full-length OP-1, the "common utility" requirement is not met, thus the Markush group is improper. Applicants respectively disagree. Pursuant to MPEP 806.02 titled "Patentability Over the Prior Art Not Considered", "[f]or the purpose of a decision on the question of restriction, and for this purpose only, the claims are ordinarily assumed to be in proper form and patentable (novel and unobvious) over the prior art." By the same reason, when deciding whether a Markush group is proper or not based on the common utility and structural feature criteria, the issue of patentability (such as enablement) should not be considered.

Furthermore, Applicants have provided substantial evidence to support enablement of the other recited polypeptides in the Markush Group (see below), thus even if the "improper Markush group" objection is maintained in view of the above arguments, it should be withdrawn in view of the enablement arguments provided below. Thus, reconsideration and withdrawal of this objection is respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph – Written Description

Claim 28 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which is not adequately described in the specification. Specifically, the Office Action alleges that only full-length human and mouse OP-1 sequences meet the written description requirement, while other OP-1 proteins corresponding to sequences from alternative species, mutated sequences, allelic and splice variants do not.

Applicants have amended claim 28 and added new claims 52 - 59 to clarify the subject matter claimed. Applicants submit that amended claim 28 and its dependent claims (as well as new claims 52 - 59) meet the written description requirement.

First of all, Applicants wish to point out that although the human and mouse OP-1 sequences (and human BMP-2, -5, and - 6 sequences) are described in detail in the instant specification, they do not represent all homologs of these proteins that were already known at the time of filing. For example, other OP-1 homologs, such as dog and Xenopus OP-1, were already known at the time of filing of the instant application. To illustrate this point, Applicants hereby

submit **Exhibit A**, which lists a non-limiting number of morphogens that were already known at the time of filing. This is also in accord with MPEP 2164.05(a): "The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)." In addition, according to the *Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, ¶1, "Written Description" Requirement (2000)*, F.R. 66(4): 1099-1111, "an applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention... What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (emphasis added). Therefore, at least those morphogens additionally listed in **Exhibit A** meet the written description requirement.

Regarding what constitutes a sufficient written description for a claimed genus, such as the genus of sequences fall within the definition of the recited sequences of claim 28, Applicants wish to direct the Examiner's attention to *Regents of University of California v. Eli Lilly and Co.* 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). In that case, the Federal Circuit pointed out that "every species in a genus need not be described in order that a genus meet the written description requirement. See *Utter*, 845 F.2d at 998-99, 6 USPQ2D (BNA) at 1714 ('A specification may, within the meaning of § 112 P 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses')" (emphasis added). In addition, in view of *In re Robins*, 57 CCPA 1321, 429 F.2d 452, 456-57, 166 U.S.P.Q. (BNA) 552, 555 (CCPA 1970), "Mention of representative compounds encompassed by generic claim language clearly is not required by § 112 or any other provision of the statute. But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language" (emphasis added). See also *In re Grimme*, 47 CCPA 785, 274 F.2d 949, 952, 124 USPQ (BNA) 499, 501 (CCPA 1960) ("it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'") (emphasis added). Nevertheless, Applicants have provided the common structural characteristics

(the Cys skeleton) possessed by members of the genus, in the form of the general formula recited in the specification and the corresponding SEQ ID NOs. Therefore, there is no need to enumerate a plurality of species (specific morphogens) to describe the genus of subject morphogens. In addition, Applicants have demonstrated possession of the subject morphogens by describing representative morphogen sequences (see above).

Particularly, Applicants submit that the genus of subject morphogen sequences with at least about 60% sequence identity with residues 330-431 of human OP-1 (SEQ ID NO: 2) meets the written description requirement.

There are only 102 amino acid residues in the specified region, thus a species of any one of the recited morphogens which sequence is at least about 60% identical to human OP-1 may only have about 40 residue changes when compared to the human OP-1 sequence. There is only a limited number of sequences that actually fall within this scope of sequences. In addition, any sequence would need to satisfy the requirement of having the seven-Cys skeleton structure, further limiting the possibilities. As mentioned above, the Federal Circuit has held that "[a] specification may, within the meaning of § 112 P 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses" (*Utter v. Hiraga*, 845 F.2d at 998-99, 6 USPQ2D (BNA) at 1714). A skilled artisan can name each and every one of these sequences based on the description of the instant specification. Finally, the number of morphogens is additionally defined by the functional qualification of "said morphogen induces dendrite outgrowth in a hippocampal neuron."

Similarly, Applicants submit that the genus of subject morphogen sequences with at least about 70% sequence homology with residues 330-431 of human OP-1 (SEQ ID NO: 2) meets the written description requirement.

In addition to the arguments presented above, Applicants submit that a skilled artisan would know how to calculate sequence homology and would know what constitute conserved amino acid substitutions for sequence homology calculation purposes, especially in view of the state of the art and the disclosure of the instant application (see for example, page 20, last paragraph). Applicants wish to point out that the Dayhoff reference recited in that paragraph (*Atlas of protein Sequence and Structure*; vol. 5, suppl. 3, ch. 22, 1978) teaches what constitutes conserved amino acid sequence changes. As a skilled artisan would appreciate, the Dayhoff

reference is widely considered to be the standard for protein sequence homology analysis even today. Thus given the framework of a reference sequence, such as residues 330-431 of human OP-1 (SEQ ID NO: 2) recited in claim 52, a skilled artisan would conclude that the Applicants have *possession* of the claimed invention in view of the art of sequence homology calculation at the time of filing. On the other hand, if Applicants were required to list each and every sequence that falls within the scope, it would not only be an impossible and unnecessary task, but also be inconsistent with the controlling U.S. case law as discussed above.

And lastly, Applicants wish to draw the Examiner's attention to a few recently issued U.S. Patents directed to related subject matter, which contain allowed claims reciting the "70% homology" or the "60% identity" language.

For example, claim 1 of U.S. Pat. No. 6,407,060 (issued June 18, 2002) reads: "A method for enhancing recovery of central nervous system function in a mammal, comprising the step of: administering an effective amount of a morphogen to a mammal afflicted with a central nervous system injury selected from ischemia and trauma, wherein said morphogen comprises a dimeric protein having the property of inducing tissue-specific morphogenesis in said mammal and comprising a pair of folded polypeptides, each having an amino acid sequence having at least 70% homology with the C-terminal seven-cysteine domain of human OP-1, residues 330-431 of SEQ ID NO:5, wherein said morphogen is not transforming growth factor beta (TGF-ß); wherein the effective amount of the morphogen is first administered at least 12 hours after the onset of said injury; and wherein the administration enhances the recovery of central nervous system function in the mammal." In addition, claim 13 reads: "The method of claim 1, wherein said amino acid sequence is a sequence having greater than 60% amino acid sequence identity with the C-terminal seven-cysteine domain of human OP-1, residues 330-431 of SEQ ID NO:5."

Similarly, claim 1 of U.S. Pat. No. 6,333,312 (issued Dec. 25, 2001) reads: "A method of treating osteopenia, comprising administering systemically to a mammal a composition consisting essentially of a morphogen and a pharmaceutically-acceptable vehicle, wherein said mammal suffers from osteopenia, and wherein said morphogen comprises an amino acid sequence selected from the group consisting of a sequence: (a) having at least 70% homology with the C-terminal seven-cysteine skeleton of human OP-1, residues 330-431 of SEQ ID NO: 5; (b) having greater than 60% amino acid sequence identity with said C-terminal seven-cysteine

skeleton of human OP-1; and (c) defined by OPX, SEQ ID NO: 29, wherein said morphogen does not have the amino acid sequence of TGF-beta and wherein said morphogen stimulates endochondral bone formation in an in vivo bone assay."

Likewise, claim 1 of U.S. Pat. No. 6,399,569 (issued June 4, 2002) reads: "A method for protecting proliferating epithelial cells in a mammal from the cytotoxic effects of an agent that destroys epithelial cells, comprising the step of administering to the mammal an isolated morphogen dispersed in a biocompatible carrier, wherein said morphogen: (i) has at least 70% homology with the C-terminal seven cysteine skeleton of human OP-1, residues 38-139 of SEQ ID NO: 5; (ii) is not TGF-beta; and (iii) is capable of inhibiting lesion formation in an in vivo oral mucositis assay, and wherein said morphogen reduces the cytotoxic effects of said agent on proliferating epithelial cells when administered to said mammal."

Therefore, Applicants submit that amended claim 28 and its dependent claims, as well as new claims 52 - 59 meet the Written Description Requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. 112, first paragraph – Enablement

Claims 28-32 and 37-42 have also been rejected under 35 U.S.C. 112, first paragraph, since the specification allegedly does not enable one skilled in the art to make and use the claimed invention. In particular, the Examiner states that the present claims are not reasonably supported by the specification.

The Office Action asserts that Applicants have failed to provide enablement for morphogens other than full-length human or mouse OP-1. However, Applicants note that the Office Action acknowledged that the claimed invention is enabled both in vitro and in vivo in view of the arguments filed on May 3, 2002.

To provide evidence that the claimed invention is enabled for the full scope of morphogens, Applicants hereby submit a post-filing reference by Guo et al. (submitted herein as **Exhibit B**), which uses essentially the same conditions set forth in the specification to demonstrate that other recited morphogens, including the *Drosophila* protein 60A, possess the same ability as that of OP-1 to induce dendritic outgrowth.

Pursuant to MPEP 2164.01, "Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." Thus, the test of enablement is whether a skilled artisan can practice the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

First of all, Applicants submit that the experimental conditions of Guo et al. are *essentially identical* to those used in the Examples of the instant application (compare pages 59-60 of the specification with page 131-132 of Guo). Thus, Guo provides post-filing evidence that a number of morphogens with diverse sequences all stimulate dendritic outgrowth, under essentially the same conditions described in the instant specification. In other words, Guo demonstrates that a skilled artisan can successfully practice the claimed invention using morphogens commensurate to the full scope of the claims, without resorting to any knowledge other than that already disclosed in the specification

Secondly, Applicants submit that the instant specification is enabled to the full scope of the claimed invention. Guo demonstrates that a representative number of morphogens, especially those within the subgroup containing OP-1, OP-2, BMP-5, BMP-6 and 60A, and those within the subgroup containing BMP-2, BMP-4, and Dpp (see the last few lines of column 1, page 131, to the first few lines of column 2, page 131 in Guo), are particularly effective in stimulating dendritic outgrowth. Especially worth mentioning is the fact that the *Drosophila* protein 60A, which only shares about 33% overall sequence identity with human OP-1 (see **Exhibit C**), is nonetheless quite effective in stimulating dendritic growth of mammalian (rat) neurons. A close analysis of the conserved C-terminal Cys skeleton sequences (**Exhibit D**) reveals that the *Drosophila* protein 60A is about 69% identical to human OP-1 in this region, indicating that the conserved C-terminal Cys skeleton sequence is especially important for the observed common biological function. **Exhibits C and D** also indicate that the C-terminal Cys structures are the most conserved regions among all morphogens, while the more N-terminal sequences are very diverse. One extreme example is the *Drosophila* protein Dpp, which contains large numbers of amino acid sequence "insertions" at the N-terminal regions such that it is only about 40% identical to its closest relatives human BMP-2 and -4. However, it is remarkably conserved at the C-terminus so that it is about 75% identical to human BMP-2 and -4, and 58% identical to

human OP-1. The only reasonable interpretation of these data is that the conserved Cys skeleton sequence defines the common structural feature important for their common biological function. Therefore, it can be reasonably expected that other morphogens, especially those within the subgroup containing OP-1, OP-2, BMP-5, BMP-6, and 60A, and those within the subgroup containing BMP-2, BMP-4, and Dpp, will also exhibit an activity that stimulates dendritic outgrowth.

Regarding the minimal sequence identity to residues 38-139 of SEQ ID NO: 5 required for a morphogen to exhibit the claimed dendritic outgrowth activity, Applicants wish to draw the Examiner's attention to the BMP-3 data in Table 1 of Guo. According to data presented in Table 1 of Guo, BMP-3 "produced a slight but statistically significant increase in dendritic growth," (page 133, right column, lines 11-12 of Guo), although at 50 ng/ml, the effect is not very pronounced. However, this is not to be confused with non-enablement, since enablement should not be confused with the best mode. "The best mode requirement is a separate and distinct requirement from the enablement requirement of the first paragraph of 35 U.S.C. 112. *In re Newton*, 414 F.2d 1400, 163 USPQ 34 (CCPA 1969)." (MPEP 2165.02). Even if BMP-3 and its related morphogens may not be the best available morphogens for practicing the claimed invention, if it can be used to practice the claimed invention, no matter how inefficient in achieving its intended effect, it is still enabled.

Thus, if the seven-Cys skeleton sequence of BMP-3 can be just about 40-50% identical to other morphogens described in the specification (see **Exhibit D**), and still exhibit a statistically significant ability to stimulate dendritic outgrowth, then other claimed morphogens that exhibit greater sequence identity with OP-1 may be reasonably expected to exhibit at least as much, if not more, dendritic growth stimulatory activity. In view of these data, a skilled artisan would reasonably conclude that all sequences represented by the presently claimed morphogens are enabled to the full scope. Indeed, Applicants submit that the specification has enabled *beyond* the presently claimed morphogens.

Regarding partial (rather than full-length) morphogens, Applicants reiterate that the only highly conserved domain among all morphogens, from those of human to *Drosophila*, is the C-terminal seven Cys skeleton. A skilled artisan would readily understand that the most reasonable and scientifically logical conclusion is that this region is responsible for the common observed

biological function. In addition, Applicants submit U.S. Pat. No. 5,011,691 (**Exhibit E**), in which natural C-terminal Cys skeletons of a number of morphogens, as well as a few synthetic sequences ("COPs") are directly shown to exhibit the same biological activity as full-length morphogens.

Applicants also submit a second post-filing reference by Le Roux (**Exhibit F**), which demonstrates that the ability of morphogens to stimulate dendritic growth is not limited to PNS neurons (such as rat sympathetic neurons), but also applies to CNS neurons (such as cerebral cortical neurons and hippocampal neurons). Specifically, Le Roux used essentially the same concentrations of OP-1 (subject to specific culturing conditions for CNS neurons) to achieve essentially the same result in CNS neurons as that achieved in PNS neurons, demonstrating that the claimed invention is enabled to both CNS and PNS neurons.

Therefore, based on the above argument, Applicants submit that all pending claims as amended are enabled to their full-scope. Applicants respectfully request reconsideration and withdrawal of rejections on grounds of 35 U.S.C. 112, first paragraph.

Claim rejections under 35 U.S.C. 102(b)

Claim 28-32 and 46-48 also stand rejected under 35 U.S.C. 102 as being anticipated by Reuger et al., WO 94/03200, or Wang et al., WO 95/05846. Applicants respectfully traverse this rejection.

Specifically, the Office Action asserts that Reuger et al. teach morphogen-induced nerve regeneration and repair of damaged neurons and neuronal pathways. To support this view, the Office Action asserts that Reuger teaches OP-1 enhancement of neuronal cell survival (Example 3), redifferentiation including neuronal outgrowth (Figure 1B), protection from chemical trauma (Example 5), nerve gap repair (pages 97-99), and repair of neuronal pathways (claims 32-33). (all emphasis added).

To anticipate a claimed invention, a cited reference must teach each and every aspect of the claimed invention. Applicants submit that none of these teachings of Reuger are what is claimed. Especially, Reuger never mentioned the ability of morphogens to induce *dentritic outgrowth*. As a skilled artisan would understand, "neuronal survival" and "dendritic outgrowth

and synapses formation" are quite different. Survival simply means "not dying," and it implies nothing about the neuron's ability to develop further structures such as dendrites. Thus what is required for neuronal survival may be, and usually *is*, quite different from what is required for dendrite outgrowth and synapses formation. Thus the teaching that morphogens can enhance neuronal survival (such as those in Example 3 of Reuger) cannot anticipate the teaching of the instant application that morphogen can also induce dendrite outgrowth, just like the ability of morphogens to stimulate bone growth cannot anticipate their ability to enhance neuronal survival.

The Office Action alleges that Figure 1B of Reuger teaches "redifferentiation including neuronal outgrowth." Applicants submit that Figure 1B was labeled as "the ability of morphogen (OP-1) to induce transformed neuroblastoma x glioma cells (1A) to dedifferentiate to a morphology characteristic of untransformed neurons (1B)." Thus, morphogens here are disclosed as capable of inducing *redifferentiation* of a *transformed* tumor cell into neuron-like cells, rather than inducing dendrite outgrowth of normal neurons. As a skilled artisan would appreciate, redifferentiation of cells, especially transformed cells, is quite a different biological process when compared to dendrite outgrowth of normal neurons – at least there is no evidence to support that the former process (redifferentiation of transformed cells) is intimately related to the latter process. Furthermore, Figure 1B only shows neuron-like structures, but does not explicitly teach whether dendrites are formed in those cells – in fact, the extended processes in those cells look a lot like axons than dendrites.

Similarly, the ability of morphogens to protect cells from chemical trauma (Example 5) and to alleviate immune response-mediated damage (Example 10) teaches or suggests nothing about morphogen-stimulated dendrite outgrowth and synapses formation.

"Nerve gap repair" recited in Reuger appears to be regeneration of axons, rather than dendrites. As a skilled artisan would appreciate, axons are those single long appendages extended from the cell bodies of neurons, while dendrites are those short, numerous appendages concentrated at the so-called "dendritic arbor" of the cell bodies of neurons. Axons and dendrites are distinct structures of neurons serving distinct functions, and there is no evidence in the cited reference that the regulation and regeneration of these processes are the same. The burden is on the Examiner to provide such evidence if rejection on this ground is to be maintained.

Regarding "repair of neural pathways" recited in claims 32-33 of Reuger, Applicants submit that such broad generic terms do not teach or suggest the ability of morphogens in inducing dendritic outgrowth and synapses formation. Neural pathways can be damaged in numerous ways. For each particular type of damage, there can be many different mechanisms of repair. It cannot be assumed without factual evidence that "repair of neuronal pathway" simply means "stimulating dendritic outgrowth and synapses formation," because neuronal pathways can be damaged by, for example, severing of axons of neurons, and the repair of which may not be related to dendritic outgrowth at all.

The Office Action argues that Reuger teaches delivery of OP-1 to hippocampal neurons on page 100. Since "all that is required to achieve the elements recited in the preamble are 'contacting said cells with a morphogen,'" the Office Action concludes that it inherently provides for dendritic outgrowth and synapse formation of the claimed hippocampal neurons, and thus anticipates the claimed invention. Applicants respectfully disagree.

Applicants wish to draw the Examiner's attention to a recent CAFC case regarding inherent anticipation (*Elan Pharms. v. Mayo Found. for Med. Educ. & Research*, 304 F.3d 1221, CAFC, 2002). Elan Pharmaceuticals, Inc. and Athena Neurosciences, Inc. (collectively "Elan") appealed from the decision of the United States District Court for the Northern District of California, granting summary judgment in favor of the Mayo Foundation for Medical Education and Research ("Mayo"). The district court held that Elan's two patents in suit, United States Patent No. 5,612,486 for "Transgenic Animals Harboring APP Allele Having Swedish Mutation" (the '486 patent) and continuation Patent No. 5,850,003 for "Transgenic Rodents Harboring APP Allele Having Swedish Mutation" (the '003 patent), were invalid on the ground of anticipation by United States Patent No. 5,455,169 for "Nucleic Acids for Diagnosing and Modeling Alzheimer's Disease" (the Mullan patent). The Federal Circuit reversed the summary judgment on the ground that the legal requirements of anticipation were not met on the facts of record, and remanded the case for further proceedings.

The prior art Mullan patent discloses a human mutation in the APP gene that predisposes a Swedish family harboring this mutation to Alzheimer's disease. Mullan also states that the mutated gene can be transferred to a mouse that preferably will express the variant human APP, so that an animal model for studying Alzheimer's disease can be established. Mullan also

discusses the various known procedures of gene transfer, citing scientific articles as to each "approach" used to create transgenic animals. However, it is undisputed that Mullan did not produce a transgenic animal with the Swedish mutation, or determine which of the known procedures would be effective for this purpose, or suggest conditions or details of any method for successful production of the desired animal. Expert witnesses for both sides testified as to the difficulty, uncertainty, unpredictability, and low success rate of each method that has been used to create transgenic animals. The Elan patent discloses and claims a transgenic rodent expressing a human APP polypeptide having the Swedish mutation, which polypeptide is processed to ATF-betaAPP in a sufficient amount to be detectable in a brain homogenate of said transgenic rodent.

The Federal Circuit pointed out:

> Anticipation is a question of fact, as is the question of inherency. Its proof differs from that for obviousness, 35 U.S.C.S. § 103, in that prior knowledge by others requires that all of the elements and limitations of the claimed subject matter must be expressly or inherently described in a single prior art reference. The single reference must describe and enable the claimed invention, including all claim limitations, with sufficient clarity and detail to establish that the subject matter already existed in the prior art and that its existence was recognized by persons of ordinary skill in the field of the invention... ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it"). (emphasis added)

Reuger certainly does not at all describe the claimed invention (using morphogen to induce dendritic outgrowth and synaptic formation in hippocampal neurons) to place a skilled artisan in the field of the invention in possession of the claimed invention. Likewise, Reuger does not enable a skilled artisan to practice the claimed invention. A reference which does not even teach or suggest the use of morphogen in inducing dendrite outgrowth would logically fail to teach a skilled artisan *how* to make and use the claimed invention without undue experimentation.

According to the Federal Circuit:

> When anticipation is based on inherency of limitations not expressly disclosed in the assertedly anticipating reference, it must be shown that the undisclosed information was known to be present in the subject matter of the reference.
>
> Inherency cannot be based on the knowledge of the inventor; facts asserted to be inherent in the prior art must be shown by evidence from the prior art. *In re*

Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) (criticizing the "hindsight syndrome wherein that which only the inventor taught is used against its teacher"). (emphasis added)

Applicants submit that by alleging anticipation of the claimed invention by Reuger based on the common method step, the Office Action is ignoring the fact that the instant application first teaches the use of morphogens in inducing dendrite outgrowth. Thus, the Office Action impermissibly uses the inherency rejection based on the knowledge of the inventor rather than evidence from the prior art, as is required by law.

As the Federal Circuit points out:

The purpose of the rule of inherency is to accommodate common knowledge, knowledge that judges might not know but that would be known to practitioners in the field. *Finnigan Corp. v. Int'l Trade Comm'n*, 180 F.3d 1354, 1365, 51 USPQ2d 1001, 1009 (Fed. Cir. 1999).

On the law of anticipation, precedent has not improved on the words of Judge Learned Hand: "No doctrine of the patent law is better established than that a prior patent or other publication to be an anticipation must bear within its four corners adequate directions for the practice of the patent invalidated. If the earlier disclosure offers no more than a starting point for further experiments, if its teaching will sometimes succeed and sometimes fail, if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation." *Dewey & Almy Chemical Co. v. Mimex Co.*, 124 F.2d 986, 989 (2d Cir. 1942). (emphasis added)

Applicants submit that the use of morphogen in inducing dendrite outgrowth and synapse formation is not "common knowledge" prior to the filing of the instant application, and it is not the type of knowledge that "judges might not know but that would be known to practitioners in the field." The discovery that morphogen can induce dendrite outgrowth and synapse formation certainly "enriches the store of common knowledge." On the other hand, Reuger does not even offer a skilled artisan a hint or a "starting point" for further experiments (to examine the role of morphogens in dendrite outgrowth), let alone "inform the art without more how to practice the new invention (of inducing dendrite outgrowth)." Thus Reuger cannot anticipate the claimed invention.

Reuger at best "accidentally" teaches a similar method step for pursuing a different result. Such accidental co-incidence cannot be anticipation based on U.S. case law. Applicants wish to draw the Examiner's attention to a U.S. Supreme Court decision (Tilghman v. Proctor, 102 U.S. 707, 1880). Mr. Tilghman patented a chemical process in the 1850's of great interest to the candle-making industry. The patent in question relates to the treatment of fats and oils, and is for a process of separating their component parts so as to render them better adapted to the uses of the arts. It has but a single claim, the words of which are as follows: "Having now described the nature of my said invention, and the manner of performing the same, I hereby declare that I claim, as of my invention, the manufacturing of fat acids and glycerin from fatty bodies by the action of water at a high temperature and pressure."

In the course of his testimony, Tilghman argued that "Perkins' house-warming apparatus consisting of coils of hundreds of feet of pipe containing water at the temperature of melting lead" to explain why, in his patent, he specially recommended the use of the high temperature of melting lead in applying his process to practical use.

The Supreme Court stated that: "[w]e do not regard the accidental formation of fat acid in Perkins's steam cylinder from the tallow introduced to lubricate the piston (if the scum which rose on the water issuing from the ejection pipe was fat acid) as of any consequence in this inquiry. What the process was by which it was generated or formed was never fully understood. Those engaged in the art of making candles, or in any other art in which fat acids are desirable, certainly never derived the least hint from this accidental phenomenon in regard to any practicable process for manufacturing such acids." (emphasis added). The Court further explained that "[i]f the acids were accidentally and unwittingly produced, whilst the operators were in pursuit of other and different results, without exciting attention and without its even being known what was done or how it had been done, it would be absurd to say that this was an anticipation of Tilghman's discovery."

Therefore, accidental co-incidence generated during a process intended for a different result, without the operator's "exciting attention" and without "its even being known what was done or how it had been done" is not anticipatory. In the instant case, Reuger states in page 99 that Example 11 can be used as an animal model for assessing morphogen efficacy in vivo: "[t]he in vivo activities of the morphogens described herein also are assessed readily in an

animal model as described herein." Clearly, Example 11 is only meant to assess the "in vivo activities of morphogens described herein," which does not include an activity of morphogen to induce dendrite growth and synapse formation, as is presently claimed. In view of Elan and Tilghman, Reuger cannot anticipate the claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claim 28-32 and 46-48 also stand rejected under 35 U.S.C. 102 as being anticipated by Wang et al., WO 95/05846. Applicants respectfully traverse this rejection.

Wang et al. discloses that certain morphogens can be used to induce the differentiation of astrocytes (which are not neurons), which allegedly "provide a conductive environment for axon growth, which is an important aspect of nerve regeneration." (see page 1 of Wang). Example I indicates that Balb c/SFME (serum-free mouse embryo) cells were contacted by BMP-2 to differentiate, and astrocyte markers GFAP and A2B5 were detected by immunostaining, FACS analysis, or Western blot. In the RESULT section, Wang states that "[t]reatment of SFME cells with TGF-beta1 or serum resulted in distinct morphological changes accompanied by expression of the astrocyte-specific differentiation marker GFAP." Several BMPs were also said to cause similar effects (see page 12). Thus, aside from not differentiating the effects of morphogens and TGF-beta1 (which is not a morphogen as the term is used in the specification), Wang et al. primarily discuss the differentiation of mouse embryonic cells to astrocytes (see also the paragraph bridging pages 13-14). Wang et al. provide no data to support that the alleged invention (stimulating neuron regeneration indirectly through stimulating astrocyte differentiation) in fact works, either in vitro or in vivo. The only prophetic example (Example II) is directed to peripheral nerve regeneration (not CNS neuron such as hippocampal neurons). In addition, the nerve regeneration relates to axon regeneration (see the rat sciatic nerve regeneration model on page 16), not dendritic outgrowth.

In summary, the teachings of Wang et al. are directed to a substantially different method with a substantially different purpose. For example, claim 8 of Wang et al. recites "a method for inducing growth of neural cells." However, neural growth is a generic term without a defined meaning within the context of Wang et al. The most likely interpretation is "neural proliferation," which is unrelated to what is claimed in the instant application. If it is interpreted

as growth of cell in volume, it is also unrelated to dendritic growth which is a *differentiation* event. In any case, claim 8 of Wang et al. is directed to a different purpose / result. Similarly, claims 13 and 21 recite "treating a mammal having a neural defect, neural damage or a neural condition." These are also broad generic terms that do not read on dendritic growth or synapses formation, since Wang et al. never explicitly, impliedly, or inherently teach the effect of any morphogens on dendritic growth. Thus these claims are also directed to a substantially different method.

The Office Action alleges that Wang et al. teach contacting neural cells including at the site of said defect or damage with BMP-7 (claims 8, 13, and 21). Applicants submit that Wang et al. never teach contacting neural cells with morphogens. The claims merely mention "administering to said mammal at the site of said defect or damage..." In fact, Wang et al. *teach away* from contacting neural cells with morphogens, since according to the teachings of Wang et al., it is the direct effect of morphogens on astrocytes, not neurons, that ultimately promote neuron (axon) regeneration. In view of Wang et al., a skilled artisan would not contact a neuron directly with a morphogen since he would understand that morphogen has to work through astrocytes to stimulate nerve regeneration. Based on the argument presented above, Wang cannot anticipate the claimed invention, because the teachings of Wang et al. are intended for a substantially different purpose and result, even if the ultimate action (contacting cells with morphogen) is the same. This is in parallel with the Perkins' house-warming apparatus and Tilghman's invention described above.

On the other hand, if Wang is anticipatory simply because the claims of Wang et al. contain the action of contacting cells with morphogen (or administering morphogen), then Wang et al. is anticipatory to any morphogen activity, including those as-yet unidentified activities. In fact, Wang itself would be anticipated by earlier publications teaching the use of morphogens for bone morphogenesis, since those studies invariably would involve contacting cells with morphogens.

Applicants submit that this point of view is also in accord with the controlling U.S. case law. Specifically, for inherent anticipation of **method claims**, if a claimed method comprises steps identical to those of a method practiced in the prior art, and the same result would have been achieved in the prior art method, the accidental or unwitting achievement of that result

cannot constitute anticipation. *In re Marshall*, 578 F.2d 301, 198 USPQ 344 (CCPA 1978). In *Marshall* the PTO board used the *Physician's Desk Reference* (PDR) as a basis for a rejection of the applicant's weight control process. The applicant's process involved anesthetizing certain intestinal nerve ends receptors with oxethazaine. The anesthesia inhibited the release of certain appetite stimulating hormones thereby inhibiting appetite. The PDR had disclosed that oxethazaine inhibits the release of gastrointestinal hormones, and such inhibition would be useful for treating certain gastrointestinal ailments. In reversing the Board's rejection, the court held that the PDR did not teach the use of the compound as a weight control drug. Addressing the issue of inherency, the court further stated that "[I]f anyone ever lost weight by following the PDR teachings it was an unrecognized accident. An accidental or unwitting duplication of an invention cannot constitute an anticipation." (*id.* 304) (emphasis added).

Applicants maintain that *Marshall* is controlling in the instant situation. In *Marshall*, note that the essential question with regards to inherency was not whether oxethazaine had inhibited the release of intestinal hormones in patients prior to the applicant's weight control process, or whether patients had lost weight when oxethazaine was administered to them as an anesthetic. Rather the question was whether the prior reference taught the reader that weight loss can be achieved by using oxthazaine. Thus, if the reference does not teach or suggest the claimed process, then the claimed process is new and unobvious in view of the reference.

In the instant case, to sustain anticipation by inherency, Wang et al. must teach or suggest the benefits of administering morphogens for inducing dendritic outgrowth in a manner that is not accidental or unwitting. One of ordinary skill in the art, having read Wang et al., should be able to achieve the claimed benefits by administering morphogens. Based on the above analysis and argument, Applicants assert that one of ordinary skill in the art, having read Wang et al., would not have known to use morphogens to stimulate dendritic outgrowth. Therefore, any administration of morphogens according to Wang can only be accidental and unwitting, thus non-anticipatory.

The Office Action also asserts that Wang et al. teach treatment of Alzheimer's disease with morphogen by stimulating nerve regeneration. Applicants submit that this is not what is claimed. Secondly, Applicants submit that although Alzheimer's disease affects hippocampal neurons, a broad recitation of "treating Alzheimer's disease" teaches nothing about dendrite

outgrowth and synapse formation as claimed in the instant application. Alzheimer's disease is not a disease with a single symptom of dendritic defect, thus a treatment for Alzheimer's disease may be directed to any one of its multiple defects, many of which remain uncharacterized as of today. A treatment for a specific underlying defect would not anticipate the treatment for all other underlying defects.

Thus, even if Wang et al. is enabled, it is directed to a substantially different invention, and thus cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection is respectfully requested.

New matter rejection

Claims 46-48 are rejected under 35 U.S.C. 112, first paragraph as containing new matter. Specifically, the Office Action alleges that morphogens comprising residues 292-330, 292-431, and 30-431 of SEQ ID NO: 2 do not have support in the specification.

Applicants submit that support can be found on pages 16-29, for morphogens comprising residues 292-330, 292-431, and 30-431 of SEQ ID NO: 2. Specifically, the first paragraph of page 16 describes several general "forms" of morphogens. Combined with what is already known in the art, a skilled artisan would understand that morphogens are secreted proteins synthesized as a "precursor" peptide with an N-terminal "signal peptide," which is rapidly cleaved during translation. The resulting protein contains a "pro-domain," the cleavage of which yields the mature C-terminal domain.

Page 29, second paragraph incorporates by reference PCT publication WO94/03600, which teaches on pages 10, 11, and 14 of its specification (and Figure 1) about the detailed structure of a morphogen (relevant pages submitted as **Exhibit G**):

> As illustrated in the figure (Figure 1), the proteins are translated as a precursor polypeptide sequence 10, having an N-terminal signal peptide sequence 12, (the "pre pro" region, indicated in the figure by cross-hatching), typically less than about 30 residues, followed by a "pro" region 14, indicated in the figure by stippling, and which is cleaved to yield the mature sequence 16. The mature sequence comprises both the conserved C-terminal seven cysteine domain 20, and an N-terminal sequence 18, referred to herein as an N-terminal extension, and

which varies significantly in sequence between the various morphogens. Cysteines are represented in the figure by vertical hatched lines 22.

...

The signal peptide is cleaved rapidly upon translation, at a cleavage site that can be predicted in a given sequence using the method of Von Heijne ((1986) Nucleic Acids Research 14:4683) The "pro" form of the protein subunit, 24, in Fig. 1, includes both the prodomain and the mature domain, peptide bonded together.

The PCT publication goes on to explain what is a morphogenically active OP-1:

OP-1: Refers generically to the group of morphogenically active proteins expressed from part or all of a DNA sequence encoding OP-1 protein, including allelic and species variants thereof, e.g., humanOP-1 ("hOP-1"), or mouse OP-1 ("mOP-1".) The cDNA sequences and the amino acids encoding the full length proteins are provided in Seq. ID Nos. 1 and 2 (hOP1) and Seq. ID Nos. 3 and 4 (mOP1.) The mature proteins are defined by residues 293-431 (hOP1) and 292-430 (mOP1), wherein the conserved seven cysteine skeleton is defined by residues 330-431 and 329-430, respectively, and the N-terminal extensions are defined by residues 293-329 and 292-329, respectively. The "pro" regions of the proteins, cleaved to yield the mature, morphogenically active proteins, are defined essentially by residues 30-292 (hOP1) and residues 30-291(mOP1). (emphasis added)

The above recited paragraphs are hereby amended into the specification, between the first and the second paragraphs of page 29.

Based on these information, a skilled artisan would understand that claim 46 is directed to a morphogen comprising the N-terminal extension, or part of the "mature form" of OP-1 (page 16, line 12); claim 47 is directed to a morphogen comprising the "cleaved pro-form" or the "mature form" of OP-1 (page 16, line 12); and claim 48 is directed to a morphogen comprising the "uncleaved pro-form" of OP-1 (see page 29, line 1). Therefore, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

Date: December 6, 2002

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